UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,088	03/22/2004	Mary R. Flack	225011	1687

45733 7590 03/19/2007

LEYDIG, VOIT & MAYER, LTD.
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6731

EXAMINER	
ANDERSON, JAMES D	
ART UNIT	**PAPER NUMBER**
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,088	FLACK ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-14,16 and 38-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-14,16 and 38-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 2/22/2007, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Status of the Claims

Claims 8-14, 16 and 38-43 are currently pending and are the subject of this Office Action.

Response to Arguments

Applicant's arguments filed 2/22/2007 have been fully considered but they are not persuasive.

Firstly, Applicants argue that it would not have been obvious to one of ordinary skill in the art that (-)-gossypol would be effective to treat cancer in humans based on the teachings of the cited references. Applicants argue that there is no teaching in Wu (1989) or Wu (1986) that gossypol is effective to treat cancer in humans. Applicants further argue that there is no teaching in Zhang that (-)-gossypol is effective to treat cancer in humans. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231

USPQ 375 (Fed. Cir. 1986). In the instant case, the question is not whether the reference(s) explicitly teach the treatment of cancer in humans with (-)-gossypol, but rather whether such treatment is obvious in view of the combined references.

Secondly, Applicants argue that there is a lack of specificity of (-)-gossypol as demonstrated by "other studies". Applicants point to several references wherein mice are administered racemic gossypol. Applicants assert that these references demonstrate that gossypol can only be safely and effectively administered only in a very narrow range. However, the references cited in the present rejections make it clear that gossypol can be safely administered to humans. Further, the references make it clear that (-)-gossypol is more efficacious than racemic or (+)-gossypol. For example, Band *et al.* state, "Considering the established absence of side effects in the administration of low doses of gossypol to humans, these data suggest that (-)-gossypol, alone or in combination with other drugs, may be useful clinically in the treatment of cancer of reproductive tract origin." Thus, the fact that racemic gossypol can only be safely and effectively administered in a very narrow range in mice, does not mean that (-)-gossypol has the same therapeutic index in humans. In fact, it is evident from the totality of the prior art of record that the toxicity of racemic gossypol is likely due to the presence of (+)-gossypol and that (-)-gossypol is more active than (+)-gossypol. Thus, the skilled artisan would have been imbued with at least a reasonable expectation that (-)-gossypol could be safely administered to humans while maintaining therapeutic efficacy.

Applicants assert that the combined references fail to disclose the efficacy of (-)-gossypol in the treatment of cancers in humans. Applicants further assert that the teachings regarding *in vitro* testing and/or testing in mice would not have led one of ordinary skill in the art to expect

that (-)-gossypol would be effective in treating cancers in humans. This is not persuasive because *in vitro* and *in vivo* testing are established models for evaluating anticancer activity. As such, the skilled artisan would have been imbued with a reasonable expectation that an agent effective *in vitro* and *in vivo* (against multiple cancer cell lines) would also demonstrate activity in a human. This is especially true given the fact that gossypol has been safely administered to humans as an antifertility agent.

The rejection of claims 8-14, 16 and 38-43 under 35 U.S.C. § 103 are maintained for the reasons of record and reiterated below.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 8-10, 16 and 38-43 are again rejected under 35 U.S.C. § 103(a) as being unpatentable over Wu *et al.* (Cancer Research, 1989, vol. 49, pages 3754-3758) (prior art of record) in view of Band *et al.* (Gynecologic Oncologists, 1986, vol. 23, page 261) (prior art of

record) and Zhang *et al.* (Acta Academiae Medicinae Sinicae, 1985, vol. 7, pages 384-387) (cited by applicants in IDS filed 5/1/2006).

The instant claims are drawn to the treatment of cancer in humans comprising the administration of (-)-gossypol.

Wu *et al.* disclose the *in vitro* and *in vivo* antitumor activity of gossypol in human SW-13 adrenocortical carcinoma cells (Abstract). It is disclosed that gossypol was known in the art to exhibit a broad spectrum of activities, including antitumor activity. For example, gossypol was known to lengthen the survival of 10-12 week old mice bearing mouse mammary adenocarcinoma and was effective against cells originating from a rat testicular tumor (page 3754). The authors demonstrate that gossypol inhibits the proliferation of SW-13 adrenocortical carcinoma cells *in vitro* (Figure 2). Further, gossypol caused a decrease in the cumulative tumor surface area of SW-13 tumors in mice (Figure 7). Only two deaths were observed in the gossypol-treated mice, compared to ten deaths in the control group (page 3756, left column). Tumor prevalence and tumor size were both decreased in the gossypol-treated group of mice (Tables 2 and 3). The authors conclude, "These data suggest that gossypol may provide a beneficial effect in patients with adrenocortical carcinoma by decreasing the overall tumor burden and prolonging their duration of survival" (page 3758). The reference thus provides one skilled in the art with the motivation to administer gossypol to humans to treat cancer.

Band *et al.* disclose that low oral doses of gossypol is used as an effective male oral contraceptive with the only detectable side effect being hypokalemia. The reference thus demonstrates that gossypol can be safely administered to humans. The authors studied the cytotoxic effect of gossypol on reproductive cancer cell lines of ovarian, testicular and

gestational origin. Cancer cell lines were significantly more sensitive to gossypol than normal human cells of high mitotic activity, fibroblast cell lines, and PHA-stimulated lymphocytes. The tumor growth inhibitory activity of gossypol is "primarily attributable to the (-)-isomer which is 3.6 –9.3 times more potent than the (+)-isomer". The reference thus provides the skilled artisan with the motivation to administer (-)-gossypol as opposed to racemic gossypol. The authors conclude (emphasis added):

> "Considering the established absence of side effects in the administration of low doses of gossypol to humans, these data suggest that (-)-gossypol, alone or in combination with other drugs, may be useful clinically in the treatment of cancer of reproductive tract origin."

The reference thus provides further motivation to administer gossypol to humans to treat cancer.

Zhang *et al.* is provided as evidence that (-)-gossypol was effective in another preclinical model of anticancer activity. The reference discloses that (-)-gossypol inhibited the cell growth, DNA synthesis, and cell division of HeLa cell cultures, whereas (+)-gossypol had no effect. The effective concentration of (-)-gossypol was 2-fold less than that of racemic gossypol, suggesting that the antitumor activity of racemic gossypol is due to the (-)-isomer (Abstract). The reference thus provides one skilled in the art further motivation to administer (-)-gossypol to treat cancer.

In the absence of a showing of unexpected results commensurate in scope with the claims, the instantly claimed methods would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

In the instant case, the prior art establishes that gossypol: 1) can be safely administered to humans in low oral doses; 2) is an effective antitumor agent *in vivo* and *in vitro*; and 3) is more effective as the (-)-isomer than the (+)-isomer. The prior art does not explicitly disclose the administration of gossypol to humans to treat cancer. However, one skilled in the art would recognize that the models of antitumor activity disclosed in the references are often used to discover new chemotherapeutic agents. As such, the skilled artisan would have been imbued with at least a reasonable expectation that administration of (-)-gossypol to a human having cancer would be effective in treating said cancer. While antiproliferative and antitumor activity *in vitro* and *in vivo* models does not always correlate with activity in humans, the skilled artisan would have been imbued with a reasonable expectation that (-)-gossypol would be effective in treating human cancers.

It is apparent from the prior art that administration of gossypol to humans was known to be safe (Band *et al.*). Thus, the administration to humans instantly claimed would have been *prima facie* obvious. It is also clear that gossypol was known to be an effective antitumor agent in preclinical models of cancer (Wu *et al.* and Zhang *et al.*). Thus, the treatment of cancer with gossypol would have been *prima facie* obvious. With respect to the administration of (-)-gossypol, it is clear from the prior art that one skilled in the art would have known that (-)-gossypol is more effective than (+)-gossypol (Band *et al.* and Zhang *et al.*). As such, it would have been *prima facie* obvious to administer (-)-gossypol to treat cancer. This is especially true given that (-)-gossypol was known to be effective in inhibiting the cell growth, DNA synthesis,

and cell division of HeLa cell cultures as disclosed in Zhang *et al.* as well as being effective *in vivo* as disclosed in Wu *et al.*

Thus, the skilled artisan would have had the motivation to administer (-)-gossypol to humans to treat cancer as well as a reasonable expectation of success in treating said cancer.

Claims 11-14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Wu *et al.*, Band *et al.* and Zhang *et al.* as applied to claims 8-10, 16 and 38-43 above and further in view of Wu *et al.* (Clin. Pharmacol. Ther., 1986, vol. 39, pages 613-618) (prior art of record).

Instant claims 11-14 recite a specific blood concentration of (-)-gossypol as well as doses and administration routes of (-)-gossypol.

Wu *et al.* (1989), Band *et al.* and Zhang *et al.* disclose as discussed *supra*. Wu *et al.* (1986) disclose pharmacokinetic studies of racemic, (+)- and (-)-gossypol in humans and dogs (Abstract). (-)-Gossypol was administered to humans at a dose of 20 mg (page 614, left column). Mean plasma levels of (-)-gossypol are shown in Figure 2. These levels fall within the instantly claimed range. In view of the Wu *et al.* disclosure, it would have been *prima facie* obvious to modify the administration routes and doses of (-)-gossypol to effect the optimal combination of pharmacokinetics and efficacy in the treatment of cancer in humans. Such optimization of dosing schedule, administration routes and doses is routine in the art of chemotherapy.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson, Ph.D.
Patent Examiner
AU 1614

March 13, 2007

Phyllis Spivack
PHYLLIS SPIVACK
PRIMARY EXAMINER 3/14/07